polymer soluble in water and an inert polymer insoluble in water; said intermediate layer(s) (c) disposed over said layer (b) that covers the inert nucleus; and

(d) an external layer comprising an enteric coating disposed over said intermediate layer(s) (c).--

Remarks

The Office Action of July 25, 2001 has been carefully considered and reconsideration of the application as amended is respectfully requested.

Claims 2-25 are pending in the application. Claims 1-24 were rejected. Claim 1 has been cancelled. Claims 2-15 and 19-23 have been amended. New claim 25 has been added. Support for the amendments and new claim can be found in general throughout the specification. More specifically, support for claim 25 can be found on page 5, lines 15-30 of the specification. Amendments to claims 2-15 and 19-23 were to correct dependencies.

The amendments to the claims are to expedite the prosecution by eliminating prolonged arguments over matters that are not of concern to our client regarding the patent application and are not directed to the patentability of the claims. They should therefore have no effect on the application of the doctrine of equivalents to the newly amended claims.

Claim Rejections - 35 U.S.C. Section 112, second paragraph

Claims 1-24 were rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claims the subject matter which Applicant regards as the invention.

Claim 1 has been cancelled and replaced with new claim 25, which addresses the issues raised by the Examiner.

All claims as amended are believed to be sufficiently definite to satisfy the dictates

of 35 U.S.C. 112, second paragraph.

Claim Rejection - 35 U.S.C. 102

Claims 1-21 were rejected under 35 U.S.C. 102(b) as being anticipated by Sachs et al. (U.S. Patent No. 5,945,124). Claims 1-24 were rejected under 35 U.S.C. 102(e) as being anticipated by Sachs et al. (U.S. Patent No. 5,945,124) or Sachs et al. (U.S. Patent No. 6,068,856).

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference", *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ.2d 1051, 1053 (Fed. Cir. 1987).

The present invention relates to a pellet comprising an acid labile benzimidazole compound, wherein the pellet comprises (a) an inert nucleus; (b) a layer disposed over said inert nucleus, comprising an acid labile benzimidazole compound, an inert, non-alkaline polymer soluble in water and one or more pharmaceutically acceptable inert excipients; (c) one or more intermediate layers that comprise: (i) an inert, non-alkaline coating, formed of an inert, non-alkaline polymer soluble in water and one or more pharmaceutically acceptable inert excipients; and (ii) a system of modified release that comprises an inert, non-alkaline polymer soluble in water and an inert polymer insoluble in water; said intermediate layer(s) (c) disposed over said layer that covers the inert nucleus; and (d) an external layer comprising an enteric coating disposed over said intermediate layer(s) (c).

U.S. Patent No. 5,945,124 and U.S. Patent No. 6,068,856 describe an oral pharmaceutical composition of pantoprazole in pellet form which contains an alkaline core with all or part of pantoprazole, an intermediate layer formed from a water insoluble release-slowing film former and an outer enteric coating.

The present invention is not anticipated by U.S. Patent No. 5,945,124 or by U.S. Patent No. 6,068,856 because the cited prior art does not teach or suggest an inert core

coated with an active layer comprising an acid labile benzimidazole compound, an inert, non-alkaline polymer soluble in water and one or more pharmaceutically acceptable inert excipients as described in the present invention. In addition, U.S. Patent No.'s 5,945,124 and 6,068,856 at col. 4, lines 3-6 and 51-52 disclose that the pantoprazole must be in an alkaline salt form and is present in an alkaline tablet or pellet form. This is not required in the present invention. Therefore, it is respectfully requested that this rejection be withdrawn.

Claim Rejection 35 U.S.C. 103(a)

Claims 1-24 were rejected under 35 U.S.C. 103(a) as being unpatentable over Sachs et al. (U.S. Patent No. 5,945,124) or Sachs et al. (U.S. Patent No. 6,068,856).

The Examiner further rejects the present invention as being obvious over U.S. Patent No. 5,945,124 in view of Paradissis et al (U.S. Patent No. 5,445,829) or U.S. Patent No. 6,068,856 in view of Paradissis et al. (U.S. Patent No. 5,445,829). The Examiner relies on Paradissis et al. for teaching capsules comprising fast and slow release layered pellets to provide both a quicker onset of action and a prolonged duration of action.

The Examiner alleges that it would have been obvious to one skilled in the art at the time of the invention to provide mixtures of pellets having different release profiles in an effort to provide quicker release of the active agent while also providing prolonged release of the active agents.

To establish prima facie obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art, *In re Royka*, 490 F.2d 981, USPQ 580 (CCPA 1974).

As stated above, the pellet of the present invention comprises an active layer disposed over an inert nucleus, comprising an acid labile benzimidazole compound, an inert, non-alkaline polymer soluble in water and one or more pharmaceutically acceptable

inert excipients.

The present invention is nonobvious over the cited prior art because U.S. Patent No. 5,945,124 or U.S. Patent No. 6,068,856 do not teach or suggest all the claim limitations of the present invention. Namely, U.S. Patent No. 5,945,124 and U.S. Patent No. 6,068,856 do not teach the use of an active layer of benzimidazole disposed over an inert nucleus. These patents also teach that pantoprazole must be in an alkaline salt form and is present in an alkaline tablet or pellet form.

U.S. Patent No. 5,445,829 does not correct the deficiencies of the primary references. U.S. Patent No. 5,445,829 describes an extended release pharmaceutical formulation in the form of particles, which are formed by a core and a coating of extended release. These particles are different from the pellets of the present invention in that the particles do not have an enteric coating as described in the present invention and the core material of the formulations of U.S. Patent No. 5,445,829 is formed by a mixture of a solvent, an active ingredient and inert particles.

Furthermore, that there is no suggestion or motivation in U.S. Patent No. 5,445,829 to use the extended release formulation described in U.S. Patent No. 5,445,829 in a pellet composition comprising benzimidazole as an active ingredient as described in the present invention.

Therefore, one skilled in the art at the time of the invention would not look to combine the cited prior art references to make the pellet with the system of modified release of the present invention.

In light of the above, Applicants submit that all rejections of record have been overcome. Applicants accordingly submit that the application is now in condition for allowance and respectfully request action in accordance therewith.

Respectfully submitted,

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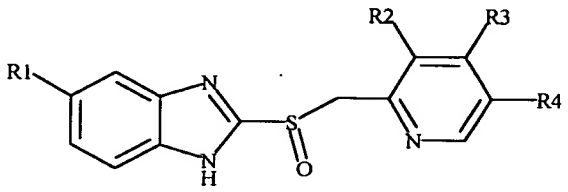
2. (Amended) A pellet according to claim 25 [1, in which] wherein said one or more intermediate layers (c) comprise one or more layers of an inert, non-alkaline coating and one or more layers of a system of modified release. [that comprises an inert, non-alkaline polymer soluble in water and an inert non-alkaline polymer insoluble in water.]

3. (Amended) A pellet according to claim 25 [1] wherein[,] the inert, non-alkaline coating[, formed of an inert, non-alkaline polymer soluble in water and one or more pharmaceutically acceptable inert excipients,] and the system of modified release [that comprises an inert, non-alkaline polymer soluble in water and an inert non-alkaline polymer insoluble in water,] are mixed in a single layer.

4. (Amended) A pellet according to claim 25 [1], in which said one or more intermediate layers (c) comprise a mixture of one or more layers of inert, non-alkaline coating, and one or more layers of said system of modified release that comprises an inert, non-alkaline polymer soluble in water and an inert [, non-alkaline] polymer insoluble in water, and one or more layers of a mixture of inert, non-alkaline coating, and said system of modified release that comprises an inert, non-alkaline polymer soluble in water and an inert [non-alkaline] polymer insoluble in water.

5. (Amended) A pellet according to claim 25 [1], wherein the inert, non-alkaline coating, formed of an inert, non-alkaline polymer soluble in water and one or more pharmaceutically acceptable inert excipients is disposed over the layer (b)[;], wherein the layer (b) [comprising] comprises the system of modified release that comprises an inert, non-alkaline polymer soluble in water and an inert [, non-alkaline] polymer insoluble in water which is disposed over the layer of the inert, non-alkaline coating; and the layer (d) is disposed over the layer formed by the system of modified release comprising an inert non-alkaline polymer soluble in water and an inert [non-alkaline] polymer insoluble in water.

6. (Amended) A pellet according to claim 25 [1] wherein said acid labile benzimidazole compound is a compound of formula (I)



(I)

wherein

R^1 is hydrogen, methoxy or difluoromethoxy[,];

R^2 is methyl or methoxy[,];

R^3 is methoxy, 2,2,2-trifluoromethoxy or 3-methoxypropoxy[,]; and

R^4 is hydrogen or methyl.

7. (Amended) A pellet according to claim 25 [1] wherein said acid labile benzimidazole compound is selected from the group consisting of omeprazole, lansoprazole, [and] pantoprazole[.] and mixtures thereof.

8. (Amended) A pellet according to claim 25 [1] wherein[,] said inert, non-alkaline polymer soluble in water, present in the layer (b) is selected from hydroxypropylmethylcellulose (HPMC) and hydroxypropylcellulose (HPC).

9. (Amended) A pellet according to claim 25 [1], wherein[,] said inert, non-alkaline polymer soluble in water of the inert, non-alkaline coating, present in the intermediate layer(s) (c) is hydroxypropylmethylcellulose (HPMC).

10. (Amended) A pellet according to claim 25 [1] wherein[,] said inert, non-alkaline polymer soluble in water of the system of modified release, present in the one or more intermediate [layer(s)] layers (c) is hydroxypropylmethylcellulose (HPMC).

11. (Amended) A pellet according to claim 25 [1] wherein[,] said inert [non-alkaline] polymer insoluble in water of the system of modified release, present in the one or more intermediate [layer(s)] layers (c) is ethylcellulose or a copolymer of ammonium methacrylate.

12. (Amended) A pellet according to claim 25 [1] wherein[,] said external layer (d) comprises a gastro-resistant polymer, a plasticizer and one or more pharmaceutically acceptable inert excipients.

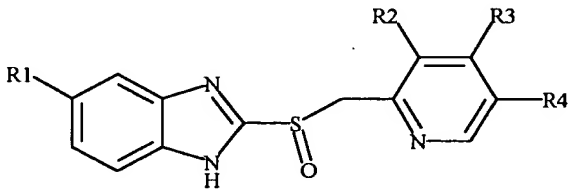
13. (Amended) A method for obtaining a gastro-resistant pellet of modified release that contains as an active ingredient an acid labile benzimidazole compound, that comprises:

(i) applying an aqueous suspension of an acid labile benzimidazole compound, an inert, non-alkaline polymer soluble in water, and one or more pharmaceutically acceptable inert excipients to cover an inert nucleus;

(ii) applying one or more intermediate layers, separated or mixed among themselves that contain (i) an inert, non-alkaline coating, formed of an inert, non-alkaline polymer soluble in water and one or more pharmaceutically acceptable inert excipients; and (ii) a system of modified release that comprises an inert, non-alkaline polymer soluble in water and an inert [non-alkaline] polymer insoluble in water, a plasticizer and an anti-tack agent, separated or mixed; and

(iii) covering said intermediate layer or layers with an aqueous suspension that comprises a gastro-resistant polymer, a plasticizer and one or more pharmaceutically acceptable inert excipients to create an external layer of enteric coating.

14. (Amended) A method according to claim 13 wherein said acid labile benzimidazole compound is a compound of formula (I)



(I)

wherein

R^1 is hydrogen, methoxy or difluoromethoxy[,];

R^2 is methyl or methoxy[,];

R^3 is methoxy, 2,2,2-trifluoroethoxy or 3-methoxypropoxy[,]; and

R^4 is hydrogen or methyl.

15. (Amended) A method according to claim 13 wherein said acid labile benzimidazole compound is selected from the group consisting of omeprazole, lansoprazole, [and] pantoprazole[.] and mixtures thereof.

19. (Amended) A method according to claim 13 wherein[,] said inert [non-alkaline] polymer insoluble in water, comprised in the system of modified release, present in the suspension applied in step (ii) is ethylcellulose or a copolymer of ammonium methacrylate.

20. (Amended) A composition of modified release that comprises one or more pellets of claim 25 [1].

21. (Amended) A composition according to claim 20, wherein the [in which] one or more [of the] pellets have the same release profile of the benzimidazole.

22. (Amended) A composition according to claim 20, wherein the [in which] one or more [of the] pellets have a different release profile of the benzimidazole.

23. (Amended) A composition according to claim 20, further comprising a mixture of (I) pellets with a quick release profile and (ii) pellets with a slow release profile[,] in a ratio [(i):(ii), by weight, lying] between 10:90 and 90:10.